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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,782	11/12/2003	Ping Jiang	312762004100	7794

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EXAMINER	
SANG, HONG	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,782	JIANG ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2 and 5-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Jiang et al.

1. Applicant's response filed on 3/5/2007 is acknowledged. Claims 1, 2 and 5-12 are pending. New claim 12 is added. Claims 3 and 4 are cancelled. Claims 1, 7, 10 and 11 are amended.

2. Claims 1, 2, and 5-12 are under examination.

Response to Arguments

3. The rejection of claims 1, 2, 5-11 and new claim 12 under 35 U.S.C. 103(a) as being unpatentable over Hadjantonakis et al. in view of Rashidi et al. (Clin. Exp. Metastasis 2000, 18: 57-60) and Trumper et al. (Blood, 1993, 81(11): 3097-3115) is maintained.

The response states that Hadjantonakis teaches mechanically separating a sample of cells from tissue where the sample, which contains both desired and undesired cells, is then enzymatically dissociated into individual cells and the desired cells, which are fluorescent, are separated using flow cytometry from undesired cells, which are not fluorescent. The response states that the invention of the applicants, on the other hand, is to label the desired cells as they reside in the tissue, and then to use the fluorescence as a guide to individually remove the desired cells away from the cells that are not desired and do not fluoresce. The response states that Trumper teaches separation cells that are no longer in the tissue. The response states that there is no reasonable motivation can be found to combine these documents. The response

states that no reason is given to why the additional limitation of claim 11 would be obvious over the cited documents.

Applicants' arguments have been carefully considered but are not found persuasive. Claim 1 as currently amended recites the active steps: mechanically, using expression of a first fluorescent protein in the desired cells as a guide, separating from the sample of tissue one or more desired living cells from undesired cells in the surrounding tissue, thereby recovering one or more desired living cells separate from any undesired cells. Hadjantonakis et al. teach a method of isolating live GFP reporter-expressing cells (cells are labeled while they are still residing in the tissue) from complex tissue by dissociation of the heterogeneous pool into single cells and subsequent flow sorting using GFP as a guide (page 56, Fig. 4). Trumper et al. teach microsurgical separation of one or more desired living cells based on cell surface staining and/or cell morphology (see Figure 1, page 3098, last paragraph, and page 3099, 1st paragraph). In the absence of specific definition for the term "mechanical separation" in the instant specification, the flow sorting of Hadjantonakis et al. and the microsurgical separation of Trumper et al. are considered as mechanical separation. Moreover, as indicated in the previous office action, because the claims as currently written do not limit the separation to a single step, i.e. picking one or more living cells directly from a tissue, the combination of Hadjantonakis and Trumper et al. teach every limitation of the claims.

Applicants appear to argue that the instant invention is to separate one or more individual desired living cells directly from the tissue where the tissue is still contained in

the living animal (see claim 10), i.e. directly from the body of the living animal (see new claim 10). However, the specification teaches only separating the desired cells,using the fluorescence as a guide, by flow cytometry or by microsurgicla technique (see page 2, paragraph [0006], and page 7, paragraph [0022]), which appear to be the same as the method of Hadjantonakis and Trumper et al. The specification does not disclose how to separate a single living cell directly from a tissue while tissue is still contained in a living animal i.e. directly from body of a living animal. Based on the disclosure of the specification, the invention of separating cells by flow sorting or microsurgical method are indeed obvious over the prior art.

Moreover, one skilled in the art would have been motivated to combine the teaching of Hadjantonakis and Trumper et al. because the microsurgical method of Trumper et al. is an alternative method to flow sorting to separate individual cells.

The reason why claim 11 is obvious over the prior art was given on page 5, 1st paragraph of the office action mailed on 6/19/09. Hadjantonakis et al. teach a method of simultaneously isolating multiple different GFP-reporter-exprssing cells using mutually exclusive reporters e.g. yellow and cyan fluorescent reporters (see pge 57, Figure 5 and 2nd paragraph, left column). Moreover, Hadjantonakis et al. teach that the cell populations defined by single or combinatorial reporter expression can also be flow sorted and segragated from one another in order to obtain specific populations of cells (see Fig.5).

Because of these reaons, the rejection is deemed proper and therefore, is maintained.

4. The rejection of claims 1, 6, 7, 10 and new claim 12 under 35 U.S.C. 102(b) as being anticipated by Schindler (Nature Biotechnology, 1998, Aug., 16: 719-720) is maintained.

The response states that Schindler does not teach the claim limitation of isolating living cells and Schindler teaches separation dead cells from fixed tissues. The response states that Schindler teaches the use of laser beams and does not describe mechanical separation. The response states that there is no sufficient description in Schindler to understand what this method is. The response states that the reference incorparated in Schindler' article i.e. the Cytometry article, teach isolating living cells using ACAS method, which does not teach using fluorescence as a guide and does not teach isolating cells from surrounding tissue.

Applicants' arguments have been carefully considered but are not persuasive. Schindler teaches that the laser-based ACAS system can be used for isolating the living cells from living tissue (see middle column, 2nd paragraph). Schindler provided sufficient description on how the method works (see page 719, right column, middle section), which comprises a): attachment of the tissue sections of interest to a thermoplastic film onto which they then bind and grow, wherein the film is adhered to a tissue culture plate and is specially treated to absorb the laser light; b) cutting the cells using a laser light, wherein as the laser beam circumscribe the desired cell(s), it cuts through and heats the cut edges of the thermoplastic film, which then melted and "weld" to the tissue culture plate; c): isolating individual cells/cell groups from tissue sections, wherein cells are isolated on "rafts" or "cookies" that remain attached to the tissue-

culture plate, the surrounding "contaminating" cells are separated from the desired cell(s) by manually pealing the unwelded film containing the unselected cells from the tissue culture plate (see page 719, right column). Schindler discloses selection, isolation and analysis of living cells from tissues expressing green fluorescent protein (GFP) chimeras and subsequent analysis of function or expression cloning of isolated GFP-containing cells (see page 719, right column), therefore, Schindler teaches using GFP as guide to select and separate cells. Because the specification does not specifically define the term "mechanically", the use of laser to separate cells is considered as a mechanical method. Moreover, it is the disclosure of Schindler's reference that is used in the instant rejection, whether or not the Cytometry article teaches the limitation of the claims is irrelevant to the instant rejection.

Because of these reaons, the rejection is deemed proper and therefore, is maintained.

5. The rejection of claims 1, 2, 5-11 and new claim 12 under 35 U.S.C. 103(a) as being unpatentable over Hadjantonakis et al. in view of Rashidi et al. (Clin. Exp. Metastasis 2000, 18: 57-60) and Schindler (Nature Biotechnology, 1998, Aug., 16: 719-720) is maintained.

The response states that cited references do not teach every limitation of the claims. The response states that Schindler deals cell culture, not intact tissue samples. The response states that Schindler does not employ mechanical separation means to obtain individual cells, but rather laser-mediated killing of undesired cells. The response

states that there is no motivation to combine the cited reference since Hadjantonakis suggested flow-cytometry as a perfectly satisfactory separation method and Schindler does not offer any particular advantages. The response states that no reason is given to why the additional limitation of claim 11 would be obvious over the cited documents.

Applicants' arguments have been carefully considered but are not persuasive. The reasons that Hadjanonakis et al. and Schindler et al teach every limitation of the claims have been set forth above (see paragraphs 3 and 4).

Schindler's laser separation has at least two advantages over Hadjanonakis et al. First, Schindler's laser separation allows separating single living cells directly from the tissue sample without using the enzyme to digest the tissue, therefore, Schindler's method would minimally affect the cells to be isolated. Secondly, Schindler's laser separation provides contamination free isolation of living cells from tissue slices (see page 720, middle column). As such, one skilled in the art would have been motivated to combine the teachings of Hadjanonakis and Schindler to arrive the instant invention.

The reason why claim 11 is obvious over the prior art was given on page 5, 1st paragraph of the office action mailed on 6/19/09. Hadjantonakis et al. teach a method of simultaneously isolating multiple different GFP-reporter-exprssing cells using mutually exclusive reporters e.g. yellow and cyan fluorescent reporters (see pge 57, Figure 5 and 2nd paragraph, left column). Moreover, Hadjantonakis et al. teach that the cell populations defined by single or combinatorial reporter expression can also be flow sorted and segragated from one another in order to obtain specific populations of cells (see Fig.5).

Because of these reasons, the rejection is deemed proper and therefore, is maintained.

6. Claims 1, 2 and 5-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hadjantonakis et al. in view of Rashidi et al. (Clin. Exp. Metastasis 2000, 18: 57-60) and Bio-Rad Microscience (Press Release 0901brm02.rls, 10/15/2001).

The response states that the Bio-Rad method is a laser cutting method and does not suggest fluorescence. The response states that no mechanical recovery of individual cells is described in Bio-Rad method. The response states that there is no motivation to combine the cited reference. The response states that no reason is given to why the additional limitation of claim 11 would be obvious over the cited documents.

Applicants' arguments have been carefully considered but are not persuasive. Bio-Rad teaches the Clonis workstation, a non-contact microdissection system for work with live cells. Using Clonis workstation, it is possible to isolate live, anchorage dependant cells from mixed cultures, and to perform secondary cutting of tissue sections (both fixed and living) placed on top of the film. Because the specification does not specifically define the term "mechanically", the use of laser to separate cells is considered as a mechanical method. While Bio-Rad's reference does not suggest fluorescence, this limitation is taught by Hadjantonakis et al. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Bio-Rad's laser separation has at least two advantages over Hadjanonakis et al. First, the laser separation allows separating single living cells directly from the tissue sample without using the enzyme to digest the tissue; therefore, the method would minimally affect the cells to be isolated. Secondly, the Clonis workstation is a non-contact microdissection system for work with live cells, therefore, provides contaminant-free isolation. As such, one skilled in the art would have been motivated to combine the teachings of Hadjanonakis and Bio-Rad laser separation to arrive the instant invention.

The reason why claim 11 is obvious over the prior art was given on page 5, 1st paragraph of the office action mailed on 6/19/09. Hadjantonakis et al. teach a method of simultaneously isolating multiple different GFP-reporter-exprssing cells using mutually exclusive reporters e.g. yellow and cyan fluorescent reporters (see pge 57, Figure 5 and 2nd paragraph, left column). Moreover, Hadjantonakis et al. teach that the cell populations defined by single or combinatorial reporter expression can also be flow sorted and segragated from one another in order to obtain specific populations of cells (see Fig.5).

Because of these reasons, the rejectin is deemed proper and therefore, is maintained.

Conclusion

7. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
April 16, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER